A Practical Overview of Drug Interactions

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Ontario Poison Information Centre

Institute for Clinical Evaluative Sciences (ICES)

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Drug-Drug Interaction (DDI):

Effect of one drug enhanced or diminished by use of another
**Definition**

- **Drug-Drug Interaction (DDI):**
  - **Effect** of one drug enhanced or diminished by use of another

- **Classification:**
  - **Pharmacokinetic**
    - Drug X changes level of Drug Y
Definition

- **Drug-Drug Interaction (DDI):**
  - Effect of one drug enhanced or diminished by use of another

- **Classification:**
  - **Pharmacokinetic**
    - Drug X changes level of Drug Y
  - **Pharmacodynamic**
    - Drug X does not change level of Drug Y
Characteristics of DDIs

- Innumerable
- “Potential interactions” are common
Potential drug–drug interactions in the medication of medical patients at hospital discharge

Potential Drug Interactions and Duplicate Prescriptions Among Cancer Patients

Cancer patients receive unnecessary medications for common prescribing.

Prescriptions with potential drug interactions dispensed at Swedish pharmacies in January 1999: cross sectional study

The growing use of pharmacological agents means that drug interactions are of increasing interest for public health. Monitoring of potential drug interactions may improve the quality of drug prescribing and dispensing, and it might form a basis for education focused on appropriate prescribing.

Participants, methods, and results

In a cross sectional study, we analysed all prescriptions...
Potential DDIs at Hospital Discharge
Egger et al *Eur J Clin Pharm* 2003

- Retrospective; n=500 prescribed ≥ 2 meds
  - 747 potential DDIs identified in 300 patients

<table>
<thead>
<tr>
<th>Potential drug–drug interaction</th>
<th>Potential adverse effect</th>
<th>Severity</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor + diuretic</td>
<td>Hypotension</td>
<td>Moderate</td>
<td>53 (13.2)</td>
</tr>
<tr>
<td>Aspirin 100 mg + ACE inhibitor</td>
<td>Decreased antihypertensive effect</td>
<td>Moderate</td>
<td>40 (10.0)</td>
</tr>
<tr>
<td>Aspirin + clopidogrel</td>
<td>Increased bleeding risk</td>
<td>Minor</td>
<td>32 (8.0)</td>
</tr>
<tr>
<td>Beta-adrenergic blocker + antidiabetics</td>
<td>Increased risk of hypoglycemia, hyperglycemia, or hypertension</td>
<td>Moderate</td>
<td>23 (5.7)</td>
</tr>
<tr>
<td>Beta-adrenergic blocker + calcium channel blocker</td>
<td>Hypotension, bradycardia</td>
<td>Moderate or major</td>
<td>22 (5.5)</td>
</tr>
<tr>
<td>Potassium-sparing diuretics + ACE inhibitor</td>
<td>Hyperkalaemia</td>
<td>Major</td>
<td>21 (5.2)</td>
</tr>
<tr>
<td>NSAID + antihypertensive drugs</td>
<td>Decreased antihypertensive effect</td>
<td>Minor or moderate</td>
<td>20 (5.0)</td>
</tr>
</tbody>
</table>
Characteristics of DDIs

- Innumerable
- “Potential interactions” are common
- Little known about real-world consequences
Characteristics of DDIs

- Innumerable
- “Potential interactions” are common
- Little known about real-world consequences
- Avoidable
Case 1

- 72 y.o. woman with coronary disease, diabetes, hypertension
  - Develops symptoms of UTI
    - Prescribed SMX/TMP DS one tablet twice daily
  - 4 days later:
    - found confused at 5:00 am
    - generalized seizure
    - husband calls 911
What happened?

- Blood glucose 0.9 mM
- Patient was taking glyburide 10 mg BID
  - Glyburide metabolized by cytochrome P450
    - isoform 2C9 (a.k.a. “CYP2C9”)
  - SMX and TMP both inhibit CYP2C9
    - ↑ glyburide levels = ↑ insulin release
The cytochrome P450 system

- A group of different enzymes that:
  - metabolize different drugs
    - ‘substrates’
  - can be turned off
    - ‘inhibitors’
  - can be “revved up”
    - ‘inducers’
### The CYP 2C9 “short list”

<table>
<thead>
<tr>
<th>CYP 2C9 Substrates</th>
<th>CYP 2C9 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>sulfonylureas</td>
<td>SMX/TMP</td>
</tr>
<tr>
<td>(S)-warfarin</td>
<td>metronidazole</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>fluvoxamine, fluoxetine</td>
</tr>
<tr>
<td></td>
<td>fluconazole</td>
</tr>
<tr>
<td></td>
<td>amiodarone</td>
</tr>
</tbody>
</table>
Glyburide and SMX-TMP – Risk of Hypoglycemia

<table>
<thead>
<tr>
<th>Table 3. Association Between Hospital Admission for Hypoglycemia and Use of Co-trimoxazole in Patients Receiving Glyburide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. (%) Exposed</strong></td>
</tr>
<tr>
<td><strong>Cases</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Hospitalization Within 1 Week of Exposure to Second Drug</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td>Amoxicillin†</td>
</tr>
<tr>
<td>Hospitalization Within 2 Weeks of Exposure to Second Drug</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td>Amoxicillin†</td>
</tr>
<tr>
<td>Hospitalization Within 3 Weeks of Exposure to Second Drug</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
</tr>
<tr>
<td>Amoxicillin†</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.
* Multivariate analysis adjusted for factors in Table 1.
† Comparable noninteracting drug for comparison.
Case 2

- 52 y.o. male smoker
  - BMI 35
  - LDL-C 5.6 mM
    - on simvastatin

- Decides to go on a diet

- 2 weeks later:
  - Severe myalgias; 4/5 quadriceps
  - CK 22,000
Grapefruit Diet

Loss 10 Pound in 12 days with Grapefruit Diet

Grapefruit Diet Introduction?

The Grapefruit diet is designed to help jumpstart your weight loss program. It is possible to lose up to 10 pounds in 12 days. The best part is it is achieved without starvation. You will be eating normal meals at normal times.

Grapefruit diet is carried out over 12 days and involves the consumption of grapefruit or grapefruit juice with each meal. Low in calories, fat free and full of vitamin C, grapefruit acts as a catalyst to enhance the fat burning process and accelerate weight loss. Pink grapefruit also contributes beta-carotene which help to reduce the cholesterol level and build a healthy heart.

The Promise of Grapefruit Diet: Loose 10 pounds in 12 days with Grapefruit Diet.

What is in grapefruit diet?

It consists of complete menu for breakfast, lunch, dinner and even come with bedtime snack. The menu consist a list of easily available foods that you can easily be obtain from any kitchen. The Grapefruit Diet is designed to help overweight people lose large amounts of weight in shortest possible timeframe. If you follow the diet exactly it is possible to lose up to 10 pounds in 12 days.

Grapefruit Diet Plan
Statins and grapefruit

Statin-associated rhabdomyolysis triggered by grapefruit consumption

Jens P. Dreier, MD; and Matthias Endres, MD
What happened?

- Simvastatin is metabolized by CYP3A4
- Grapefruit juice blocks CYP 3A4 in gut wall
  - $\uparrow$ absorption of simvastatin $> 8$-fold
CYP 3A4:
Liver and small intestine
CYP 3A4 Substrates

- Some statins
  - atorvastatin, lovastatin, simvastatin

- CCBs
  - all of them

- Some benzos
  - diazepam, alprazolam, triazolam

- Miscellaneous
  - carbamazepine, cyclosporine
  - sildenafil, vardenafil
CYP 3A4 Inhibitors

- Macrolides
  - erythromycin, clarithromycin
  - (not azithro)

- CCBs
  - verapamil, diltiazem

- Amiodarone

- Several antiretrovirals
  - ritonavir, nelfinavir & others
CYP 3A4 Inducers

- Anticonvulsants
  - carbamazepine
  - phenobarbital
  - phenytoin
  - topiramate
- Dexamethasone
- Tamoxifen
- St. John’s Wort
Acute heart transplant rejection due to Saint John’s wort

Frank Ruschitzka, Peter J Meier, Marko Turina, Thomas F Lüscher, Georg Noll

We report here acute rejection in two transplant patients due to a metabolic interaction of St John’s wort and ciclosporin.

St John’s wort (Hypericum perforatum) is a folk remedy frequently used for the treatment of skin injuries, burns, and neuralgia. Recently, it has gained a reputation as an effective treatment for depression. However, the mechanism of action of the postulated antidepressant effects is unclear.

A 61-year-old heart transplant patient was admitted for elective endomyocardial biopsy. Orthotopic heart transplantation had been done 11 months earlier because of end-stage ischaemic cardiomyopathy (figure, A). Subsequently, the patient had an event free course (International Society of Heart and Lung Transplantation [ISHT], grading 0 or 1A) and was maintained on a standard immunosuppressive regimen of ciclosporin (125 mg twice daily), azathioprine (100 mg daily) and low dose corticosteroids (7.5 mg daily). Ciclosporin plasma levels remained stable throughout the year. Three weeks before admission the patient started self-medication with St John’s wort because of mild depression. The standardised St John’s wort extract LI160 (sold under the brand name Jarsin® containing 900 µg hypericin) was taken at a dose of 300 mg three times daily (further chemical analysis of the drug was not done). On admission, the patient had nonspecific fatigue, but was otherwise feeling well. Physical

Ciclosporin concentrations in two patients after heart transplantation

Treatment with St John’s wort was associated with a drop in ciclosporin values below the therapeutic range and acute transplant rejection.
Case 3

- 64 y.o. with metastatic breast Ca
  - on Codeine Contin 150 mg BID
- Rx paroxetine for symptoms of depression
  - 2 days later → markedly worse bone pain
What happened?
What happened?

- Codeine is a prodrug

\[
\text{Codeine} \quad \xrightarrow{\text{CYP 2D6}} \quad \text{Morphine}
\]

\[
\Theta
\]

paroxetine
CYP 2D6

- Metabolizes 15-20% of drugs
- Highly polymorphic
  - Functionally absent in 7-10%
    - “Poor metabolizers”
  - Greatly increased activity in some
    - “Ultrarapid metabolizers”
    - Scandinavia: 1%
    - Italy: 10%
    - Greece: 12%
    - Saudi Arabia: 33%
    - Ethiopia: 37%
<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>donepezil, galantamine</td>
<td>amiodarone</td>
</tr>
<tr>
<td>carvedilol, metoprolol</td>
<td>fluoxetine, paroxetine</td>
</tr>
<tr>
<td>codeine ***</td>
<td>terbinafine</td>
</tr>
<tr>
<td>tamoxifen ***</td>
<td></td>
</tr>
</tbody>
</table>

*** = prodrug
Case 4

- 92 y.o. woman
  - independent, lives alone
  - PMH atrial fibrillation, penicillin allergy

- Arrives in emergency feeling unwell x 2d
  - recent Rx for clarithromycin 500 mg BID
Rate 28  Slow junctional rhythm, rate 28
PR   Atrial premature complex
QRS 154  Left bundle branch block
QT  672
QTc 459

--AXIS--
P  lead
QRS -21
T  166
What happened?
P-glycoprotein (P-gp)

- Membrane glycoprotein
  - first identified in chemoresistant cancer cells

- Expressed in
  - gut
  - kidney
  - bile canaliculi
  - BBB

- P-gp:
  - a “natural defense mechanism”
# P-glycoprotein

<table>
<thead>
<tr>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>digoxin</td>
<td>macrolides</td>
<td>rifampin</td>
</tr>
<tr>
<td>loperamide</td>
<td>amiodarone</td>
<td>dexamethasone</td>
</tr>
<tr>
<td>diltiazem</td>
<td>antifungals</td>
<td>St. John’s wort</td>
</tr>
<tr>
<td>cyclosporine</td>
<td>verapamil</td>
<td></td>
</tr>
<tr>
<td>chemo (various)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dabigatran etexilate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- 40 healthy volunteers
  - V 120 mg 1h before DE
    - AUC ↑ 143%
    - Cmax ↑ 179%
- Largely abolished by giving DE 2 h before verapamil
### Macrolides and Digoxin

**Gomes et al CP&T 2009**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cases n/N</th>
<th>Controls n/N</th>
<th>Adjusted odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarithromycin</td>
<td>55/1,659</td>
<td>16/6,439</td>
<td><strong>14.83</strong> (7.89–27.86)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>19/1,659</td>
<td>15/6,439</td>
<td>3.69 (1.72–7.90)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>6/1,659</td>
<td>7/6,439</td>
<td>3.71 (1.10–12.52)</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>≤5/1,659</td>
<td>13/6,439</td>
<td>0.85 (0.21–3.41)</td>
</tr>
</tbody>
</table>

**Between-drug comparisons:**

- Clarithromycin vs. azithromycin: 4.00 (1.06–15.73)
- Clarithromycin vs. erythromycin: 4.02 (1.49–10.81)
- Erythromycin vs. azithromycin: 0.99 (0.24–4.18)
Case 5

- 42 y.o. woman with recurrent idiopathic VTE
  - INR consistently 2.0 to 3.0

- LRTI
  - Family physician prescribed Levaquin

- 1 week later
  - Painless hematuria
  - INR 9.2
What happened?

- (Hint: it’s not Levaquin)

Blood Coagulation, Fibrinolysis and Cellular Haemostasis

Paracetamol (acetaminophen) warfarin interaction: NAPQI, the toxic metabolite of paracetamol, is an inhibitor of enzymes in the vitamin K cycle

Henk H. Thijssen¹, Berry A. Soute², Lily M. Vervoort¹, Jolanda G. Claessens³

Departments of ¹Pharmacology and ²Biochemistry, University of Maastricht, Maastricht, The Netherlands
³Anticoagulation Center Maastricht, Maastricht, The Netherlands
Acetaminophen + Warfarin (?)

\[ \text{II, VII, IX, X} \xrightarrow{\gamma\text{-carboxylase}} \text{IIa, VIIa, IXa, Xa} \]

Acetaminophen metabolite

Vit K hydroquinone

Vit K epoxide

Warfarin
Interactions with warfarin: The 5 A’s

- **Amiodarone**
- **Antibiotics**
  - sulfamethoxazole / trimethoprim
  - metronidazole
- **Antidepressants**
- **Antiplatelets**
- **Analgesics**
  - NSAIDs
  - acetaminophen
Less Is More

Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

Morten L. Hansen, MD, PhD; Rikke Sørensen, MD; Mette T. Clausen, MSc Pharm; Marie Louise Fog-Petersen, MSc Pharm; Jakob Raunso, MD; Niels Gadsbøll, MD, DMSc; Gunnar H. Gislason, MD, PhD; Fredrik Folke, MD; Søren S. Andersen, MD; Tina K. Schramm, MD; Steen Z. Abildstrøm, MD, PhD; Henrik E. Poulsen, MD, DMSc; Lars Køber, MD, DMSc; Christian Torp-Pedersen, MD, DMSc

![Graph showing hazard ratios for different combinations of therapy](image)

**Figure 3.** Hazard ratios (HRs) for the risk of nonfatal (n=12,191) and fatal (n=1,381) bleeding associated with the use of warfarin, aspirin, clopidogrel, and combinations of these drugs. CI indicates confidence interval.
Case 6

- 82 y.o. woman
- PMH:
  - CAD, HTN, GERD, OA, DM, CKD
- Meds
  - Metoprolol 50 mg BID
  - Aspirin 325 mg OD
  - Lisinopril 20 mg OD
  - Spironolactone 25 OD
  - Rofecoxib 12.5 mg OD
  - Septra DS 1 BID (recent UTI)
- Arrives in ED with anorexia & malaise x 1/52
Why did this happen?

- **Medications**
  - ramipril
  - trimethoprim
  - rofecoxib
  - spironolactone

- **Disease**
  - diabetes
  - renal insufficiency

"YOU PROBABLY SHOULDN'T MIX YOUR VIAGRA WITH YOUR PROPECIA."
Spironolactone Rx in Ontario

NEJM 2004;351:543-51
Admissions involving ↑ K⁺
Hyperkalemia: The Usual Suspects

Renal disease
ACE Inhibitors
ARBs
K+ supplements
Spironolactone
Amiloride
Triamterene
The “Unusual Suspects”

Diabetes  
NSAI Ds  
Septra  
β-blockers  
Salt substitutes
Co-trimoxazole and $↑K^+$

Trimethoprim

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Admission for $↑K^+$ Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-trimoxazole</td>
<td>6.7 (4.5 to 10.0)</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>0.8 (0.4 to 1.5)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>1.4 (0.9 to 2.2)</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>1.1 (0.6 to 2.0)</td>
</tr>
<tr>
<td>Amoxicillin (reference)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Amiloride

Antoniou et al. *Arch Int Med* 2010
Co-trimoxazole and $\uparrow K^+$

... with spironolactone
Case 7

- 42 y.o. man
  - PMH: depression (citalopram 20 mg / day)
- Presents 12 hours after starting new medication for low back pain
- O/E:
  - Agitated, sweating, flushed
  - T 38.2  HR 115  SBP 150
  - Spontaneous and inducible clonus
  - Hyperactive reflexes
Figure 2. Findings in a Patient with Moderately Severe Serotonin Syndrome.

Hyperkinetic neuromuscular findings of tremor or clonus and hyperreflexia should lead the clinician to consider the diagnosis of the serotonin syndrome.
Tramadol
(Ultram™, Zytraml™, Ralivia™)

- Marketing
  - “Dual mechanism of analgesia”
  - “Low abuse potential”

- Reality
  - Parent drug blocks 5-HT and NE reuptake
  - Metabolite (“M1”) binds to μ receptor

- Adverse effects
  - Opioid side effects
  - Seizures
  - Serotonin syndrome
Avoiding DDIs in clinical practice
Avoiding DDIs

1. Commit a ‘short list’ of drugs to memory
   - Common “precipitants”
     - antibiotics
     - SSRIs
     - verapamil, diltiazem
     - amiodarone
     - tramadol
     - antiretrovirals
Avoiding DDIs

2. Be especially wary in patients taking high-risk drugs
   - warfarin
   - dabigatran
   - digoxin
   - sulfonylureas
   - statins
   - CCBs
   - Misc.
     - anticonvulsants, lithium, theophylline, immunosuppressants
3. When possible, choose safer alternative
   - macrolides → azithro
   - β-lactams
   - pravastatin, rosuvastatin
   - citalopram, venlafaxine
Avoiding DDIs

4. Use one pharmacy
5. External resources
   - www.drug-interactions.com
Avoiding DDIs

4. Use one pharmacy
5. External resources
   - www.drug-interactions.com
6. Informed patient = safer patient
Recap

- Background

- Several avoidable “high-value” DDIs
  - glyburide + SMX-TMP
  - statins + grapefruit juice
  - digoxin + clarithromycin
  - codeine + paroxetine
  - warfarin + acetaminophen
  - ACE inhibitors / spironolactone + SMX-TMP
  - tramadol + SSRIs

- Avoidance strategies